Docket No. 10806-151

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Lynne W. Moore

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Andreas CASTAN	:	Paper No.:
Serial No.:	09/732,638	:	Group Art Unit: 1634
Filed:	December 8, 2000	:	Examiner: B. Sisson
For:	**Production of Peptides**		

APPEAL BRIEF

Box AF
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by certificate of mailing on December 23, 2002.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee of the present application, Pharmacia AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellant, the Appellant's undersigned legal representative or the assignee which will directly effect or be directly effected by or having a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 1-20 and 22-28 are pending in the present application. Claims 1-20 and 22-28 stand rejected and are the subject of the present appeal. Claim 21 has been cancelled. A complete copy of the pending claims 1-20 and 22-28 on appeal is set forth in the Appendix.

IV. STATUS OF AMENDMENT FILED SUBSEQUENT TO REJECTION ON APPEAL

Appellants have appealed the Examiner's final rejection of the claims set forth in the Official Action dated July 25, 2002. A Request for Reconsideration Under 37 C.F.R. 1.116, without claim amendments, was submitted by Certificate of Mail on October 25, 2002. Submitted herewith is an Amendment Under 37 C.F.R. 1.116 which requests amendment of claim 1 to correct a typographical error, to thus place claim 1 in better form for appeal. The Attached Appendix incorporates the amendment to claim 1. However, if the Examiner should refuse entry of the Amendment, a revised Appendix will be provided.

V. SUMMARY OF THE INVENTION

The present invention is directed to methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. (page 4, lines 25-27). The methods provide improved recombinant peptide quality and yield with the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed. (page 4, lines 20-23).

According to independent claim 1, the method is directed to production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed

and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. The oscillation has a wave period of from about 1 to about 30 minutes. The microorganism is a biological host selected from the group consisting of bacteria, yeast and animal cell and the cultivation conditions remain aerobic.

Claims 2-7 and 22-28 further define the methods of claim 1. According to claim 2, the organic carbon source is glucose. According to claim 3, the microorganism is E. Coli. According to claim 4, the oscillation feed has a square wave pattern. According to claim 5, the oscillation feed has a sinus pattern. According to claim 6, the recombinant peptide is growth hormone. According to claim 7, the recombinant peptide is human growth hormone.

According to claim 22, the oscillation feed has a square wave function of +/- 30% of standard and a wave period of 1 minute. According to claim 23, the oscillation feed has a wave amplitude of from about +/- 5% to +/- 60% of standard. According to claim 24, the oscillation variation in stirring speed is +/- 20% of standard with a square wave period of 1 minute. According to claim 25, the oscillation variation in stirring speed of claim 22 is +/- 20% of standard with a square wave period of 1 minute.

According to claim 26, the microorganism is *E. coli* and the recombinant peptide is human growth hormone. According to claim 27, the recombinant peptide comprises recombinant human growth hormone, immune interferon, tissue plasminogen activator, or human insulin. According to claim 28, the oscillation feed and/or oscillation variation in stirring speed is from about +/- 5% to +/- 60% of standard.

Claims 8, 9, 11, 13 and 17 further define the methods of claim 2. According to claim 8, the microorganism is *E. Coli.* According to claim 9, the oscillation feed has a square wave pattern. According to claim 11, the oscillation feed has a sinus wave pattern. According to

claim 13, the recombinant peptide is growth hormone. According to claim 17, the recombinant peptide is human growth hormone.

Claims 10, 12, 14 and 18 further define the methods of claim 3. According to claim 10, the oscillation feed has a square wave pattern. According to claim 12, the oscillation feed has a sinus wave pattern. According to claim 14, the recombinant peptide is growth hormone. According to claim 18, the recombinant peptide is human growth hormone.

Claims 15 and 19 further define the methods of claim 4. According to claim 15, the recombinant peptide is growth hormone. According to claim 19, the recombinant peptide is human growth hormone.

Claims 16 and 20 further define the methods of claim 5. According to claim 16, the recombinant peptide is growth hormone. According to claim 20, the recombinant peptide is human growth hormone.

VI. ISSUES ON APPEAL

There are four issues on appeal for review by the Board, as follows:

A. The rejection of claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 under 35 U.S.C. §102(a), (e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Nakamura et al, U.S. Patent No. 5,912,113.

B. The rejection of claims 1-5, 8-12, 22, 23 and 28 under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al in view of Gschaedler et al, *Biotechnology and Bioengineering*, Vol. 63, No. 6, pages 712-720 (June 1999).

C. The rejection of claims 6, 7, 13-20, 26 and 27 under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al and Gschaedler et al, as applied to claims 1-5, 8-12, 22, 23, and 28, and further in view of Honjo et al, U.S. Patent No. 5,824,502.

D. The rejection of claims 24 and 25 under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al and Gschaedler et al, as applied to claims 1-5, 8-12, 22, 23, and 28, and further in view of Bhattacharya et al, *Enzyme and Microbial Technology*, 20:355-360 (1977) and Takahashi et al, U.S. Patent No. 5,399,771.

VII. GROUPING OF THE CLAIMS

A. With respect to the above noted issue A on appeal, Appellant concedes that claims 1 and 2 stand or fall together; claims 4 and 9 stand or fall together; and claims 5 and 11 stand or fall together. However, Appellant submits that claims 4 and 9; claims 5 and 11; claim 22; claim 23; and claim 28 are independently patentable from claim 1 from which they directly or indirectly depend. Reasons in support of the independent patentability of these claims are set forth below.

B. With respect to the above noted issue B on appeal, Appellant concedes that claims 1-3 and 8 stand or fall together; claims 4 and 9 stand or fall together; and claims 5 and 11-12 stand or fall together. However, Appellant submits that claims 4 and 9; claims 5 and 11-12; claim 22; claim 23; and claim 28 are independently patentable from claim 1 from which they directly or indirectly depend. Reasons in support of the independent patentability of these claims are set forth below.

C. With respect to the above noted issue C on appeal, Appellant concedes that claims 6 and 13-16 stand or fall together and claims 7, 17-20 and 26 stand or fall together. However, Appellant submits that claims 6 and 13-16; claims 7, 17-20 and 26; and claim 27

are independently patentable from one another. Reasons in support of the independent patentability of these claims are set forth below.

D. With respect to the above noted issue D on appeal, Appellant submits that claims 24 and 25 are independently patentable and reasons in support of their independent patentability are set forth below.

VIII. ARGUMENTS

As will be set forth in detail below, the methods as defined by claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 are not anticipated by and are nonobvious over and patentably distinguishable from Nakamura et al, U.S. Patent No. 5,912,113. The methods of claims 1-5, 8-12, 22, 23 and 28 are nonobvious over and patentably distinguishable from Nakamura et al in view of Gschaedler et al, *Biotechnology and Bioengineering*, Vol. 63, No. 6, (June 1999). The methods of claims 6, 7, 13-20, 26 and 27 are nonobvious over and patentably distinguishable from Nakamura et al and Gschaedler et al, as applied to claims 1-5, 8-12, 22, 23, and 28, and further in view of Honjo et al, U.S. Patent No. 5,824,502. Finally, the methods of claims 24 and 25 are nonobvious over and patentably distinguishable from Nakamura et al and Gschaedler et al, and further in view of Bhattacharya et al, *Enzyme and Microbial Technology*, 20:355-360 (1977) and Takahashi et al, U.S. Patent No. 5,399,771. Accordingly, the rejections of claims 1-20 and 22-28 under 35 U.S.C. §§102 and/or 103 should be reversed. Favorable action by the Board is respectfully requested.

A. The Invention

As set forth above, the present invention is directed to methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The methods

provide improved recombinant peptide quality and yield with the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed. According to independent claim 1, the method is directed to production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. The oscillation has a wave period of from about 1 to about 30 minutes. The microorganism is a biological host selected from the group consisting of bacteria, yeast and animal cell. The cultivation conditions remain aerobic.

B. The Claimed Methods are not Anticipated By and are Nonobvious Over Nakamura et al

The methods as defined by claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 are not anticipated by and are nonobvious over and patentably distinguishable from Nakamura et al.

1. The Rejection

The Examiner asserted that Nakamura et al disclose a method of culturing a microorganism in a batch culture under aerobic environment whereby glucose is added to the culture media in an oscillating manner. Specifically, the Examiner asserted that Nakamura et al teach that glucose may be added to the culture media at less than 2 minutes as well as less than or equal to 30 minutes; yeast as well as bacterial cultures may be used; and the oscillation speed is considered to have a wave amplitude that ranges from +/- 5% to +/- 60% of standard. The Examiner also asserted, in the Advisory Action of November 14, 2002, that Nakamura et al disclose culturing cells to where there is exhaustion of the carbon source, in some embodiments, however, such step is performed to determine the feed rate. In addition, the Examiner asserted that Nakamura et al teach feeding continuously, and further, that it is

possible to easily control the substrate concentration in the cultivation to the level as low as below 5 g/l, further below 3 g/l.

2. Nakamura et al do not Anticipate the Claimed Methods

Nakamura et al, discussed at page 3 of the present application, disclose methods for controlling a carbon source concentration at a constant low level of under 5 g/l in an aerobic cultivation medium by monitoring and adjusting the time period and the feeding rate of the carbon source feed solution (column 7, lines 9-11). Nakamura et al further disclose that the time period for adding the carbon source feed solution is selected within such a range that the activity of a microorganism for consuming the carbon source does not change greatly (column 5, lines 11-16). Nakamura et al also disclose that the feeding rate of the carbon source feed solution is determined by "exhaustion of the carbon sources" in the culture medium (column 4, lines 19-22 and 36-40).

Appellant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out without exhaustion of the organic carbon source, as required by claim 1. Rather, as discussed above, Nakamura et al teach a method for aerobically culturing a microorganism, wherein the feeding rate of the carbon source feed solution is determined by the "exhaustion of the carbon sources" in the culture medium contained in the cultivation vessel. As described in the present specification at page 5, lines 8-10, "the carbon source should never be exhausted during the process and there is no need for measuring its concentration during cultivation." In fact, Nakamura et al teach away from the present invention wherein the carbon source is not exhausted as Nakamura et al disclose throughout the specification that the carbon source is constantly measured during cultivation to determine when the carbon source is exhausted. (Column 4,

lines 5-9 and 37-43, column 5, lines 17-19, 31-33, and 65-67, and column 6, lines 1-9, 33-44, and 47-51).

In addition to the teachings of the specification, Figures 4 A-C of Nakamura et al illustrate the constant measurement of the conditions in the feed culture of Example 1 to determine when the carbon source is exhausted. In Figures 4 A-C, the y-axis represents, respectively, the dissolved oxygen concentration; pH; and sugar concentration in the fermentor, while in each figure the x-axis represents increasing time. As shown in these Figures, the concentration of the carbon source is constantly measured because an increase in either the dissolved oxygen concentration as shown in Figure 4A or the pH as shown in Figure 4B signifies exhaustion of the carbon source. As illustrated in Figure 4C, this exhaustion of the carbon source initiates a new feeding rate for a subsequent addition of the feed solution to the culture medium.

As noted above, the Examiner acknowledges that in some embodiments, Nakamura et al disclose culturing of cells to where there is exhaustion of the carbon source, such step being performed to establish a feed rate. However, the Examiner also asserts that the feeding may performed "continuously or intermittently" and therefore if the feeding is continuous there cannot be exhaustion of the carbon source. This assertion by the Examiner clearly disregards the teachings of Nakamura et al in that exhaustion of the carbon source is necessary to determine the feeding rate for each addition of the carbon source feed solution as shown in Figure 4C. The Examiner also asserts that the claimed methods do not preclude that there never be a time when the substrate has been exhausted. The Examiner's position is contrary to the express limitation of claim 1 that the method occurs "without exhaustion of the organic carbon source." Thus, Appellant finds no teaching, suggestion or reference by Nakamura et al of the presently claimed methods since the methods of Nakamura et al require

constant monitoring of the carbon source in the cultivation medium in order to determine the feeding rate by "exhaustion of the carbon source".

Moreover, Appellant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, particularly with an oscillation having a waver period of from about 1 to about 30 minutes. As further described in the present specification at page 4, lines 20-24, "the glucose feed was varied in oscillation feed and/or the stirring speed was performed in oscillation variation in a fed-batch cultivation...The word oscillation used here can also be described as pulses or by up and down-shifts." Rather, Nakamura et al teach that the carbon source is to be maintained at a constant level during each addition period, i.e., first addition, second addition, etc., as disclosed for example at column 7, lines 9-11.

The Examiner asserts that Figure 8 of Nakamura et al depicts via bar graph that the time periods and rate of glucose addition take on a square wave pattern and that the line graph, which depicts glucose concentration, takes on a sinus wave pattern. It is unclear to which Figure the Examiner refers, as there is no Figure 8 in the Nakamura et al reference. As both Figures 4C and 5 depict sugar concentration over a period of time, each figure will be addressed independently. As noted in detail above, Figure 4C illustrates conditions for the feed culture in Example 1. The line graph of Figure 4C does not depict addition of the carbon source in oscillation, but rather depicts the resultant carbon source concentration in the fermentor obtained by monitoring the exhaustion of the carbon source and adjusting the level feeding rate based upon this exhaustion. Moreover, the bar graph of Figure 4C does not

depict addition of the carbon source in oscillation, but rather depicts the constant level of feeding rates during specific 3 hour addition periods as described in Example 1.

Figure 5 depicts the state of controlling the sugar concentration, i.e., carbon source, (y axis) over a period of time, hours (x axis) in Example 1. The line graph demonstrates the carbon source concentration at nine points during the 80 hour time period and Nakamura et al's conclusion that the concentration is maintained at a low level during cultivation. Thus, the line graph does not depict addition of the carbon source in oscillation, but rather depicts the resultant carbon source concentration obtained by monitoring and adjusting the time period and feeding rate of the carbon source feed solution. Moreover, the bar graph of Figure 5 merely depicts the constant feeding rates during specific 3 hour addition periods. As disclosed in detail above, the Nakamura et al feeding rate is maintained at a constant level during each 3 hour time period. Thus, the bar graph of Figure 5 does not depict addition of the carbon source in oscillation, but rather depicts the constant level of the feeding rate during a specified time period. Therefore, Appellant finds no teaching, suggestion or reference by Nakamura et al of the presently claimed methods since Nakamura et al teach methods wherein the carbon source feeding rate to be maintained at a constant level.

Anticipation under 35 U.S.C. §102 requires the disclosure in a single prior art reference each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q. 2d 1337, 1341 (Fed. Cir. 1986). In view of the failure of Nakamura et al to disclose a method as defined by claim 1, particularly wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of organic carbon source, the reference does not disclose each element of the claims under consideration and therefore does not support a

rejection of claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 under 35 U.S.C. §102. The rejection should therefore be reversed.

3. No Prima Facie Case of Obviousness is Established

As discussed in detail above, Appellant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out "without exhaustion of the organic carbon source". Rather, Nakamura et al teach a method for aerobically culturing a microorganism, wherein the feeding rate is determined by the "exhaustion of the carbon sources" in the culture medium contained in the cultivation vessel. Nakamura et al, therefore, teach away from the present invention defined by claim 1, wherein the carbon source is not exhausted during cultivation.

Moreover, Appellant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed. As described in the present specification at page 4, lines 20-24, "the glucose feed was varied in oscillation feed and/or the stirring speed was performed in oscillation variation in a fed-batch cultivation...The word oscillation used here can also be described as pulses or by up and down-shifts." Rather, Nakamura et al exemplify, as discussed in detail above, that the carbon source is to be maintained at a constant level during each 3 hour period. While, as noted by the Examiner, Nakamura generally disclose that a feed may be continuous or intermittent, Appellant finds no further teaching or suggestion as to what is meant by intermittent specifically, Appellant finds no teaching, suggestion or reference by

Nakamura et al regarding feed or oscillation stirring, particularly wherein the oscillation has a wave period of from about 1 to about 30 minutes.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). Not only does Appellant find no teaching by Nakamura et al relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism, as defined by claim 1, Appellant finds no teaching or suggestion by Nakamura et al for modifying the methods disclosed therein to result in a method, as defined by claim 1, particularly wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed with an oscillation having a waver period of from about 1 to about 30 minutes and without exhaustion of the organic carbon source. In view of the failure of Nakamura et al to teach, suggest or recognize a method as defined by claim 1, the reference does not provide an enabling disclosure of the present invention, and therefore does not support a rejection of claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 under 35 U.S.C. §103. The rejection should therefore be reversed.

4. Claims 4 and 9 are Independently Patentable

Claim 4 recites a method according to claim 1, wherein the oscillation feed has a square wave pattern. Claim 9 recites a method according to claim 2, wherein the oscillation feed has a square wave pattern. Appellant finds no teaching, suggestion or reference in Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation of a microorganism wherein the cultivation is carried out by the addition of the

organic carbon source in oscillation feed and/or by oscillation variation of stirring speed with an oscillation having a wave period of from about 1 to about 30 minutes as recited in claim 1, and wherein the oscillation feed has a square wave pattern as recited in claims 4 and 9. Rather, as noted above, Nakamura et al teach that the carbon source be maintained at a constant level during each 3 hour addition period.

Further, Appellant finds no teaching in Nakamura et al which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the methods as recited in claims 4 and 9. Specifically, Appellant finds no teaching or suggestion in Nakamura et al, which would suggest to one of ordinary skill in the art to add the organic carbon source in oscillation wherein the oscillation feed has a square wave pattern. The Examiner asserts that Figure 8 of Nakamura et al depicts via bar graph that the time periods and rate of glucose take on a square wave pattern. As noted above, Nakamura et al do not provide a Figure 8, and the bar graphs in Figures 4C and 5 do not depict addition of the carbon source in oscillation wherein the oscillation feed has a square wave pattern. Rather, the bar graphs of Figures 4C and 5 depict the constant level of feeding rates during specific 3 hour addition periods. Therefore, Appellant finds no teaching, suggestion, or reference of the presently claimed methods since the methods of Nakamura et al teach the carbon source feeding rate to be maintained at a constant level.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, *supra*. Not only does Appellant find no teaching by Nakamura et al relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism, as defined by claims 4 and 9, Appellant finds no teaching or suggestion by Nakamura et al for modifying the methods disclosed therein to result in the methods as

defined by claims 4 and 9, particularly wherein the cultivation is carried out with the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a square wave pattern. In view of the failure of Nakamura et al to teach, suggest or recognize methods as defined by claims 4 and 9, the reference does not provide an enabling disclosure of the present invention, and therefore does not support a rejection of claims 4 and 9 under 35 U.S.C. §103. The rejection should therefore be reversed.

5. Claims 5 and 11 are Independently Patentable

Claim 5 recites a method according to claim 1, wherein the oscillation feed has a sinus pattern. Claim 11 recites a method according to claim 2, wherein the oscillation feed has a sinus wave pattern. Appellant finds no teaching, suggestion or reference in Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a sinus pattern as recited in claims 5 and 11. Rather, as noted above, Nakamura et al teach that the carbon source be maintained at a constant level during each addition period.

Further, Appellant finds no teaching in Nakamura et al which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the methods as recited in claims 5 and 11. Specifically, Appellant finds no teaching or suggestion in Nakamura et al, which would suggest to one of ordinary skill in the art to add the organic carbon source in oscillation wherein the oscillation feed has a sinus pattern. The Examiner asserts that Figure 8 of Nakamura et al depicts via line graph that the glucose concentration

takes on a sinus wave pattern. As noted above, the line graphs in Figures 4C and 5 do not depict addition of the carbon source in oscillation, wherein the oscillation feed takes on a sinus pattern. Rather, the line graphs depict the resultant carbon source concentration in the fermentor obtained by monitoring the exhaustion of the carbon source and adjusting the level feeding rate based upon this exhaustion. Therefore, Appellants find no teaching, suggestion, or reference of the presently claimed methods since the methods of Nakamura et al teach the carbon source feeding rate to be maintained at a constant level.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. Not only does Appellant find no teaching by Nakamura et al relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism, as defined by claims 5 and 11, Appellant finds no teaching or suggestion by Nakamura et al for modifying the methods disclosed therein to result in the methods, as defined by claims 5 and 11, particularly wherein the cultivation is carried out with by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a sinus pattern. In view of the failure of Nakamura et al to teach, suggest or recognize methods as defined by claims 5 and 11, the reference does not provide an enabling disclosure of the present invention, and therefore does not support a rejection of claims 5 and 11 under 35 U.S.C. §103. The rejection should therefore be reversed.

6. Claims 22, 23 and 28 are Independently Patentable

Claim 22 recites a method according to claim 1, wherein the oscillation feed has a square wave function of +/-30% of standard and a wave period of 1 minute. Claim 23 recites a method according to claim 1, wherein the oscillation feed has a wave amplitude of from

about +/-5% to +/-60% of standard. Claim 28 recites a method according to claim 1, wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard.

Appellant finds no teaching, suggestion or reference Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a square wave function of +/-30% of standard and a wave period of 1 minute (claim 22), wherein the oscillation feed has a wave amplitude of from about +/-5% to +/-60% of standard (claim 23), or wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard (claim 28). Rather, as noted above, Nakamura et al teach that the carbon source be maintained at a constant level during each addition period.

Further, Appellant finds no teaching in Nakamura et al which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the method as recited in claims 22, 23 or 28. Specifically, Appellant finds no teaching or suggestion in Nakamura et al which would suggest to one of ordinary skill in the art to add the organic carbon source in levels of oscillation, as recited in claims 22, 23 or 28. The Examiner asserts that Figure 8 of Nakamura et al depicts via bar graph that the time periods and rate of glucose take on a square wave pattern. As noted above, the line graphs in Figures 4C and 5 do not depict addition of the carbon source in oscillation, wherein the oscillation feed takes on a sinus pattern. Rather, the line graphs depict the resultant carbon source concentration in the fermentor obtained by monitoring the exhaustion of the carbon source and adjusting the level

feeding rate based upon this exhaustion. Moreover, the bar graphs in Figures 4C and 5 do not depict addition of the carbon source in oscillation wherein the oscillation feed has a square wave pattern. Rather, the bar graphs of Figures 4C and 5 depict the constant level of feeding rates during specific addition periods. Importantly, none of the Figures of Nakamura et al teach or suggest oscillation in feed rate or stirring of a period and/or amplitude as respectively recited in claims 22, 23 and 28. Therefore, Appellant finds no teaching, suggestion or reference by Nakamura et al of the presently claimed methods.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. Not only does Appellant find no teaching by Nakamura et al relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism with oscillation in feed rate or stirring of a period or amplitude, as defined by claims 22, 23, and 28, Appellant finds no teaching or suggestion by Nakamura et al for modifying the method disclosed therein to result in methods as defined by claims 22, 23 and 28, particularly wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a square function of +/-30% of standard and a wave period of 1 minute (claim 22), wherein the oscillation feed has a wave amplitude of from about +/-5% to +/-60% of standard (claim 23), or wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard (claim 28). In view of the failure of Nakamura et al to teach, suggest or recognize methods as defined by claims 22, 23, and 28, the reference does not provide an enabling disclosure of the present invention, and therefore does not support a rejection of claims 22, 23 and 28 under 35 U.S.C. §103. The rejection should therefore be reversed.

C. The Claimed Methods are Nonobvious Over Nakamura et al in view of Gschaedler et al

The methods defined by claims 1-5, 8-12, 22, 23 and 28 are nonobvious over and patentably distinguishable from Nakamura et al in view of Gschaedler et al.

1. The Rejection

The Examiner asserted that Gschaedler et al teach culturing *E. coli* where a recombinant peptide was produced. Thus, the Examiner asserted that it would have been obvious to use the bacterial culture, i.e., *E. coli*, of Gschaedler et al in the Nakamura et al method of culturing a microorganism.

2. No Prima Facie Case of Obviousness is Established

The method for the production of recombinant peptide by fed-bath cultivation of a microorganism in a bioreactor containing a medium of claim 1 is discussed in detail above, as are the deficiencies of Nakamura et al. That is, Appellant finds no teaching or suggestion in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed with an oscillation wave period of from about 1 to about 30 minutes, and wherein the cultivation is carried out "without exhaustion of the organic carbon source". These deficiencies of Nakamura et al are not resolved by Gschaedler.

Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation

variation of stirring speed and without exhaustion of the organic carbon source, as required by claim 1.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, supra. Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. In view of the failure of Nakamura et al in view of Gschaedler et al, to teach, suggest or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source as recited in claim 1, the references do not provide an enabling disclosure of the present invention and therefore do not support a rejection of claims 1-5, 8-12, 22, 23 and 28 under 35 U.S.C. §103. The rejection should therefore be reversed.

3. Claims 4 and 9 are Independently Patentable

Claim 4 recites a method according to claim 1, wherein the oscillation feed has a square wave pattern. Claim 9 recites a method according to claim 2, wherein the oscillation feed has a square wave pattern. As noted previously, Appellant finds no teaching, suggestion or reference in Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation of a microorganism wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a square wave pattern as recited in claims 4 and 9. These deficiencies are not resolved by Gschaedler.

As noted, Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a square wave pattern as recited in claims 4 and 9.

Further, Appellant finds no teaching in Nakamura et al or Gschaedler which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the methods as recited in claims 4 and 9. Specifically, as noted above, Appellant finds no teaching or suggestion in Nakamura et al or Gschaedler which would suggest to one of ordinary skill in the art to add the organic carbon source in oscillation wherein the oscillation feed has a square wave pattern.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. Not only does Appellant find no teaching by Nakamura et al or Gschaedler relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism, as defined by claims 4 and 9, Appellant finds no teaching or suggestion by Nakamura et al in view of Gschaedler for modifying the methods disclosed therein to result in the methods, as defined by claims 4 and 9, particularly wherein the cultivation is carried out with the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a square wave pattern.

In view of the failure of Nakamura et al in view of Gschaedler to teach, suggest or recognize methods as defined by claims 4 and 9, the references do not provide an enabling

disclosure of the present invention, and therefore do not support a rejection of claims 4 and 9 under 35 U.S.C. §103. The rejection should therefore be reversed.

4. Claims 5, 11 and 12 are Independently Patentable

Claim 5 recites a method according to claim 1, wherein the oscillation feed has a sinus pattern. Claim 11 recites a method according to claim 2, wherein the oscillation feed has a sinus wave pattern. Claim 12 recites a method according to claim 3, wherein the oscillation feed has a sinus wave pattern. Appellant finds no teaching, suggestion or reference in Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a sinus wave pattern as recited in claims 5, 11 and 12. These deficiencies are not resolved by Gschaedler.

While Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a sinus wave pattern as recited in claims 5, 11 and 12.

Further, Appellant finds no teaching in Nakamura et al or Gschaedler which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the methods as recited in claims 5, 11 and 12. Specifically, Appellant finds no teaching or suggestion in Nakamura et al or Gschaedler which would suggest to one of ordinary skill in

the art to add the organic carbon source in oscillation wherein the oscillation feed has a sinus pattern.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. Not only does Appellant find no teaching by Nakamura et al or Gschaedler relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism, as defined by claims 5, 11 and 12, Appellant finds no teaching or suggestion by Nakamura et al or Gschaedler for modifying the methods disclosed therein to result in the methods, as defined by claims 5, 11 and 12, particularly wherein the cultivation is carried out with by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a sinus pattern.

In view of the failure of Nakamura et al, in view of Gschaedler to teach, suggest or recognize methods as defined by claims 5, 11 and 12, the references do not provide an enabling disclosure of the present invention, and therefore do not support a rejection of claims 5, 11 and 12 under 35 U.S.C. §103. The rejection should therefore be reversed.

5. Claims 22, 23, and 28 are Independently Patentable

Claim 22 recites a method according to claim 1, wherein the oscillation feed has a square wave function of +/-30% of standard and a wave period of 1 minute. Claim 23 recites a method according to claim 1, wherein the oscillation feed has a wave amplitude of from about +/-5% to +/-60% of standard. Claim 28 recites a method according to claim 1, wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard.

Appellant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and wherein the oscillation feed has a square wave function of +/-30% of standard and a wave period of 1 minute (claim 22), wherein the oscillation feed has a wave amplitude of from about +/-5% to +/-60% of standard (claim 23), or wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard (claim 28). These deficiencies are not resolved by Gschaedler.

Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed as recited in claim 1, and with various levels of oscillation feed or stirring speed as recited in claims 22, 23 and 28.

Further, Appellant finds no teaching in Nakamura et al or Gschaedler which would suggest to one of ordinary skill in the art to modify the teachings of Nakamura et al to arrive at the methods as recited in claims 22, 23 and 28. Specifically, Appellant finds no teaching or suggestion in Nakamura et al or Gschaedler, which would suggest to one of ordinary skill in the art to add the organic carbon source with the amplitude and/or wave period of oscillation as respectively required by claims 22, 23 and 28.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the

public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). Not only does Appellant find no teaching by Nakamura et al in view of Gschaedler relating to the methods for the production of recombinant peptide by fed-batch cultivation of a microorganism as defined by claims 22, 23, and 28, Appellant finds no teaching or suggestion by Nakamura et al in view of Gschaedler for modifying the method disclosed therein to result in methods as defined by claims 22, 23 and 28, particularly wherein the cultivation is carried out with by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the oscillation feed has a square function of +/-30% of standard and a wave period of 1 minute (claim 22), wherein the oscillation feed has a wave amplitude of from about +/-5% to +/-60% of standard (claim 23), or wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/-5% to +/-60% of standard (claim 28).

In view of the failure of Nakamura et al in view of Gschaedler to teach, suggest or recognize methods as defined by claims 22, 23, and 28, the references do not provide an enabling disclosure of the present invention, and therefore do not support a rejection of claims 22, 23 and 28 under 35 U.S.C. §103. The rejection should therefore be reversed.

D. The Claimed Methods are Nonobvious over Nakamura et al in view of Gschaedler et al, and further in view of Honjo et al

The methods defined by claims 6, 7, 13-20, 26 and 27 are nonobvious over and patentably distinguishable from Nakamura et al in view of Gschaedler et al, and further in view of Honjo et al.

1. The Rejection

The Examiner further relied on Honjo et al as disclosing at length the recombinant production of human growth hormone (rhGH). The Examiner asserted that it would have been obvious to have modified the method of Nakamura et al with the recombinant production of human growth hormone, as disclosed by Honjo et al, in *E. coli*, as disclosed by Gschaedler et al.

2. No Prima Facie Case of Obviousness is Established

Claims 6, 13, 14, 15 and 16 recite methods according to claims 1-5, respectively, wherein the recombinant peptide is growth hormone. Claims 7, 17, 18, 19 and 20 recite methods according to claims 1-5, respectively, wherein the recombinant peptide is human growth hormone. Claim 26 recites a method according to claim 1, wherein the microorganism is *E. coli* and wherein the recombinant peptide is human growth hormone. Claim 27 recites a method according to claim 1, wherein the recombinant peptide comprises recombinant human growth hormone, immune interferon, tissue plasminogen activator, or human insulin.

The method for the production of recombinant peptide by fed-bath cultivation of a microorganism in a bioreactor containing a medium of claim 1 is discussed in detail above, as are the deficiencies of Nakamura et al. That is, Appellant finds no teaching or suggestion in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the cultivation is carried out "without exhaustion of the organic carbon source".

Moreover, Appellant finds no teaching or suggestion regarding methods for the production of recombinant growth hormone, as required by claims 1 and 13-a6, for the production of recombinant human growth hormone as required by claims 2 and 17-20, for the production of recombinant human growth hormone in *E. Coli* as required by claim 26, or for the production or recombinant human growth hormone, immune interferon, tissue plasminogen activator or human insulin as required by claim 27, or for the improvements provided by such methods, specifically improved quality and yield. In this regard, the Bards' attention is directed to the Examples set forth in the present specification at pages 6-8 which show the improvements of the claimed methods. Specifically, on page 8, lines 4-11, "It is clear from the experiment that the amount of rhGH (recombinant growth hormone) was much higher when glucose was added in an oscillation feed and by oscillation variation of stirring speed...It can be seen (in Figure 3) that the yield of the proper form of rhGH, i.e. 22 kDa is higher when glucose was added in an oscillation feed and by oscillation variation of stirring speed." Appellant finds no teaching or suggestion in Nakamura et al of such improvements in methods for the production of recombinant peptide, such as growth hormone, by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed. These deficiencies of Nakamura et al are not resolved by Gschaedler or Honjo et al.

Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide as specified in claims 6, 7, 13-20, 26 or 27 by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source, or the improvements thereof in yield and quality. Honjo et al

disclose a method for secretory production of recombinant human growth hormone (rhGH). However, Honjo et al fail to teach, suggest, or recognize a method for the production of recombinant peptide as specified in claims 6, 7, 13-20, 26 or 27 by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source, or the improvements thereof in yield and quality.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, supra. Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. In view of the failure of Nakamura et al in view of Gschaedler et al, and further in view of Honjo et al to teach, suggest or recognize a method for the production of recombinant peptide as defined by the present claims by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source, and the improvement in yield and quality provided thereby, the references do not provide an enabling disclosure of the present invention and therefore do not support a rejection of claims 6, 7, 13-20, 26 or 27 under 35 U.S.C. §103. The rejection should therefore be reversed.

E. The Claimed Methods are Nonobvious Over Nakamura et al in view of Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al

The methods defined by claims 24-25 are nonobvious over and patentably distinguishable from Nakamura et al in view of Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al.

1. The Rejection

The Examiner asserted that Bhattacharya et al disclose the significance on maintaining certain levels of dissolved oxygen and that oxygen levels played a critical role in increased recombinant peptide production of *E. coli*. The Examiner further asserted that Takahashi et al disclose the need to vary the speed at which a culture is stirred such that the dissolved oxygen level stays at the appropriate level, and the Examiner asserted varying the stirring speed +/- 20% of standard is considered to be the result of routine experimentation. Therefore, the Examiner concluded that it would have been obvious to have modified the method of Nakamura et al and Gschaedler et al with the aspect of varying the stirring speed as disclosed by Bhattacharya et al and Takahashi et al.

2. No Prima Facie Case of Obviousness is Established

Claim 24 recites a method according to claim 1, wherein the oscillation variation in stirring speed is +/- 20% of standard with a square wave period of 1 minute. Claim 25 recites a method according to claim 22, wherein the oscillation variation in stirring speed is +/- 20% of standard with a square wave period of 1 minute.

The method for the production of recombinant peptide by fed-bath cultivation of a microorganism in a bioreactor containing a medium of claim 1 is discussed in detail above, as are the deficiencies of Nakamura et al. That is, Appellant finds no teaching or suggestion in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, and wherein the cultivation is carried out "without exhaustion of the organic carbon source". The deficiencies of Nakamura et al are not resolved by Gschaedler et al, Bhattacharya et al and/or Takahashi et al.

Gschaedler et al disclose the use of *E. coli* as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source as required by claim 1, and fail to teach, suggest or recognize such a method wherein the oscillation variation in stirring speed is +/-20% of standard with a wave period of 1 minute as required by claims 24-25. Bhattacharya et al disclose the effects of dissolved oxygen and oxygen mass transfer on overexpression of target gene in recombinant *E. coli*. However, Bhattacharya et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon source as required by claim 1, particularly with the oscillation in stirring speed required by claims 24-25.

Finally, Takahashi et al disclose the preparation of thiomarinol B by the oxidation of thiomarinol with stirring. However, Appellants find no teaching or suggestion by Takahashi et al regarding oscillation of stirring speed, particularly as set forth in claims 24 and 25. Moreover, Takahashi et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed and without exhaustion of the organic carbon as further required by claims 24-25.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the

public, *In re Payne*, supra. In view of the failure of Nakamura et al in view of Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al, to teach, suggest or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, particularly with oscillation in stirring speed as required by claims 24 and 25, and without exhaustion of the organic carbon source, the references in combination do not provide an enabling disclosure of the present invention and therefore do not support a rejection of claims 24 and 25 under 35 U.S.C. §103. The rejection should therefore be reversed.

V. CONCLUSIONS

For the reasons set forth in detail above, the methods defined by the claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 are not anticipated by and are nonobvious over and patentably distinguishable from Nakamura et al; the methods of claims 1-5, 8-12, 22, 23 and 28 are nonobvious over and patentably distinguishable from Nakamura et al in view of Gschaedler et al; the methods of claims 6, 7, 13-20, 26 and 27 are nonobvious over and patentably distinguishable from Nakamura et al and Gschaedler et al, and further in view of Honjo et al; and the methods of claims 24-25 are nonobvious over and patentably distinguishable from Nakamura et al and Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al. Accordingly, the rejections of claims 1-20 and 22-28 under 35 U.S.C. §102 and/or 103 should be reversed. Favorable action by the Board is respectfully requested.

Respectfully submitted,

By _____

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